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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,212	06/17/2005	Olga N. Kovbasnjuk	60384(71699)	2349

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EXAMINER	
HUFF, SHEELA JITENDRA	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,212	KOVBASNJUK ET AL.	
	Examiner	Art Unit	
	Sheela J. Huff	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-9,11,12 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-9, 11-12 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 73/26/10 has been entered.

Claims 1-3, 6-9, 11-12 and 18 are pending.

The rejection under 35 U.S.C. 112, second paragraph, is withdrawn as stated in the advisory action.

The art rejection is withdrawn and re-written to further clarify the use of the primary reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 6-9, 11-12 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marcato et al Infection and Immunity vol. 70 p. 1279 (3/2002), in view of LaCasse et al Blood vol. 88 p. 1561 (1995) Strockbine et al J. Bacteriology vol. 170 p. 1116 (3/98), Accession Number 2002:397002 (3/2002), Green US 2002/0081307 and applicant's admission on page 6, lines 1-2 of the specification.

Marcato et al disclose shiga toxin 1 and its role in apoptosis. The A subunit inhibits protein synthesis thereby triggering apoptosis in lymphoma B cells in vitro. The B subunit alone also induces apoptosis but must be internalized to induce apoptosis in vitro. This is disclosed on page 1279 first (paragraph bridging first and second column) which states "that the B pentamer of STX 1 triggered apoptosis", "that ca. 100 times

more Stx1 B pentamer was required to induce apoptosis in Burkitt's lymphoma B cell line", "the Stx1 B pentamer also induces apoptosis in astrocytoma cells" and that in "HeLa cell transfected with *stx1b* subunit gene undergo apoptosis as well". The next paragraph ends with the statement that the present authors conclude that "the results our investigations into this activity which, in our laboratory, appears to be more potent in the Stx2 B than the Stx1 B subunit". In the discussion of this reference, the authors disclose a comparison of their data to data found by others (stating that "additional evidence…suggests that the Stx1 B subunit may activate a receptor-mediated signaling pathway, leading to the induction of apoptosis" (page 1284) and data provided by Nakagawa et al that "apoptosis was activated when these cells were transfected with a vector containing the tetracycline-inducible *stx1b* gene..the results suggested that the Stx 1B subunit must enter the cytoplasm of a eukaryotic cell to induce apoptosis" (page 1285 second column)) and also conclude the data presented in their (ie the authors) experiments come to a similar conclusion as Nakagawa et al. (page 1285 (first column, first full paragraph). Thus the author of the reference is agreeing with Nakagawa et al conclusion that Stx1B induces apoptosis.

This reference does not disclose the apoptosis in vivo and the limitations of claims 2, 6, 8-9, 11-12 and 18.

LaCasse et al disclose treatment of human B cell lymphoma from bone marrow in mice using Shiga-like toxin 1 (see entire reference). The reference also discloses that the toxin was administered after the cancer is present (see p. 1562, middle of first column). On page 6 of the specification, applicant admits the toxins are known to bind to

Gb3 expressing cells, therefore it is expected that the cells of the reference are Gb3 expressing cells. The toxin is administered before the spread of the tumor and therefore prior to metastasis. The tumor killing occurs by inhibition of protein synthesis (page 1561-first column).

Strockbine et al discloses that Shiga-like toxin and Shiga Toxin are over 99% homologous and that the difference between the two resides in the A subunit (see abstract).

Green discloses that Shiga-like toxin (also called verotoxin) and Shiga toxin are commonly known and the selection of one or the other is within the purview of one skilled in the art and that either toxin can be used in mammals (this reads on humans). (see summary of invention).

Accession Number 2002:397002 discloses that Gb3 is a biomarker for colon tumor cells.

In view of the disclosure of Lacasse et al which shows in vivo use of shiga-like toxin to treat human B cell lymphomas and combined with the knowledge of Strockbine et al that shiga-like toxin and shiga toxin are over 99% homologous and the only difference resides in the A subunit (ie the B subunits are the same) and since both shiga-like toxin and shiga toxin both inhibit protein synthesis which results in cell death, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention that the A subunit is what causes inhibition of protein synthesis and that the B subunit (which can also induce apoptosis in vitro thru internalization) (Marcato et al) can also be used in vivo to inhibit apoptosis with the expected benefit of treating B cell

lymphoma. This is obvious because (1) both shiga-like toxin and shiga toxin induce apoptosis, (2) the A subunit inhibits protein synthesis to induce apoptosis in vitro and therefore, in view of LaCasse et al which shows that shiga-like toxin inhibits protein synthesis in vivo to induce cell death it logically follows that it is the A subunit of shiga toxin that inhibits protein synthesis to induce apoptosis in vivo, and (3) therefore the B subunit which is identical in both the shiga-like toxin and the shiga toxin and which can induce apoptosis in vitro, that it can also induce apoptosis in vivo. Furthermore, "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). In view of this, it would have also been obvious to use other known cancer treatment, such as radiation or chemotherapeutic agents in combination with the B subunit to treat B cell lymphoma. Since Gb3 is a marker for colon caner and since the toxins bind Gb3, the B subunit can also be used to treat colon cancer.

Response to applicant's arguments

Applicant argues that "apoptosis was not observed in A subunit-free preparations of the Stx1B pentamer". Applicant is taking this statement out of context of the entire reference. This statement is found in the abstract and a more complete analysis of the data for this conclusion is on page 1280-1281. On page 1280, second column, first full paragraph under results, the reference clearly discusses that Stx2B subunit did not induce apoptosis and this was also unexpectedly found to be true of the

Stx1B subunit and these results were in Daudi Burkitt's lymphoma B cells. In the next paragraph the reference states that results in Ramos Burkitt's lymphoma B cells show that Stx2B subunit did induce apoptosis whereas the Stx1B subunit did not. The next paragraph on page 1281 discusses the discrepancies between their expectation that the Stx1B subunit would induce apoptosis and the results in both cell types where Stx1B did not induce apoptosis. The reason being that some Burkitt's lymphoma B cells are infected with Epstein-Barr virus and this alters the cells phenotype and thus decreasing the expression of CD77 (Gb3-Cer) receptor on these cells. In fact, the last sentence in the second column, partial paragraph, states that the results presented in figures 3 and 4 are "consistent with the conclusion that our inability to detect Stx B subunit-mediated apoptosis in the Daudi cells…may be been related to the lower amountof Gb3-Cer…expressed by these cell". Thus the reason that apoptosis was not observed in the A subunit free preparation of Stx1B pentamer was because the cells expressed less Gb3-Cer and these is only cell type specific. Thus, this does NOT negate the results found by others and the conclusion of the authors that the Stx1B subunit induces apoptosis, the results are going to be cell specific.

Applicant argues that the authors conclude that based on their results the apoptotic activity of the Stx2B is more potent than Stx1B. This is true. However, this statement is NOT saying that Stx1B has no apoptotic activity but this saying that the apoptotic activity is different for each Stx1B and Stx2B and Stx2B is more potent.

Applicant next argues the statements on page 1280-81 about the reference disclosing that the Stx1B shows no apoptotic activity in Ramos Burkitt's lymphoma B

cells. This has been address above but is re-iterated here. The reference on "page 1281 discusses the discrepancies between their expectation that the Stx1B subunit would induce apoptosis and the results in both cell types where Stx1B did not induce apoptosis. The reason being that some Burkitt's lymphoma B cells are infected with Epstein-Barr virus and this alters the cells phenotype and thus decreasing the expression of CD77 (Gb3-Cer) receptor on these cells. In fact, the last sentence in the second column, partial paragraph, states that the results presented in figures 3 and 4 are "consistent with the conclusion that our inability to detect Stx B subunit-mediated apoptosis in the Daudi cells…may be been related to the lower amount of Gb3-Cer…expressed by these cell". Thus the reason that apoptosis was not observed in the A subunit free preparation of Stx1B pentamer was because the cells expressed less Gb3-Cer and these is only cell type specific. Thus, this does NOT negate the results found by others and the conclusion of the authors that the Stx1B subunit induces apoptosis."

Applicant next refers to Figure 5 and the paragraph bridging pages 1281-1282. Again this paragraph deals with explaining the discrepancy between Stx1B having apoptotic activity and not having said activity in Ramos cells. This paragraph concludes with the fact that in Ramos cells that the apoptosis is mediated by activation of a caspase network.

Applicant again argues page 1285, first column, first full paragraph and implies that the Examiner has taken statement out of context. In fact, it is applicant that has taken statements out of context and not looked at all the data presented in the article

and the data presented in the state of the art. The following is taken from applicant's response:

> "Referring to this reference in context, Mercato et al teach on p. 1285 that "the data presented in a report by Nakagawa suggest that apoptosis was not triggered in HeLa/C4 or NIH 3T3 cells exposed to Stxl B subunit (and)...(a)poptosis was activated only when the cells were transfected with the *stxbl* gene, suggesting that the Stxl B subunit must enter the cytoplasm to induce apoptosis." Further, Mercato et al. teach that "the *data* in our experiments allow us to come to similar conclusions as Nakagawa et al., because **excess Stxl B subunit** inhibited initiation **of apoptosis** by both Stx **1** and Stx 2 holotoxins or the Stx2 B subunlt, presumably by access to the Gb3-Cer receptors." (p.1285; see Fig. 5B)."(emphasis added in the form of underlines).

In the above section, the authors, after a careful analysis of the data of Figure 5, agree with the conclusion of Nakagawa et al and the conclusion of Nakagawa et al was that Stx1B induces apoptosis.

Applicant also states "Mercato et al. are using the data of Nakagawa, where cells were transfected with *stxB1* gene in order to induce apoptosis, that is bypassing the normal endocytotic pathway of toxin internalization, to confirm their hypothesized mechanism of apoptotic death induced by Stx2 and Stxl and the StxB2 subunit." While this is true, this in NO WAY casts doubt on the validity of the statement that both Nakagawa et al and Mercato et al agree that Stx1B induces apoptosis.

Applicant argues that the secondary references do not cure the deficiencies of the primary reference. As stated above, the primary reference has not deficiencies.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the

grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J. Huff whose telephone number is 571-272-0834. The examiner can normally be reached on Monday-Thursday 6am to 2pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sheela J Huff/
Primary Examiner
Art Unit 1643

sjh